

AMENDMENTS TO THE CLAIMS

1. (currently amended): An isolated antibody that specifically binds to an N-terminal sequence of whole parathyroid hormone (PTH) and is capable of detecting said whole PTH at a physiological level in a mammalian sample, with a proviso that said isolated antibody avoids binding to a ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment.

2. (currently amended): The isolated antibody of claim 1, which is a monoclonal ~~antibody, or a~~ polyclonal antibody or an antibody fragment that specifically binds to whole PTH.

3. (currently amended): The isolated antibody of claim 1, which specifically binds to an epitope comprised in PTH₁₋₅, PTH₁₋₆, PTH₁₋₇, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₀, PTH₁₋₁₁, PTH₁₋₁₂, PTH₁₋₁₃, PTH₁₋₁₄, PTH₁₋₁₅ or PTH₃₋₁₂.

4. (original): The isolated antibody of claim 1, which specifically binds to the parathyroid hormone peptide human PTH₁₋₈, rat PTH₁₋₈, mouse PTH₁₋₈, bovine PTH₁₋₈, canine PTH₁₋₈, porcine PTH₁₋₈, horse PTH₁₋₈, human PTH₁₋₁₅, rat PTH₁₋₁₅, mouse PTH₁₋₁₅, bovine PTH₁₋₁₅, canine PTH₁₋₁₅, porcine PTH₁₋₁₅, or horse PTH₁₋₁₅, wherein at least four amino acids in said peptide sequence are part of a reactive portion with the antibody.

5. (currently amended): The isolated antibody of claim 1, which specifically binds to an epitope comprised in ~~PTH₁₋₅, PTH₁₋₇, PTH₁₋₈, PTH₁₋₁₀, PTH₁₋₁₁, PTH₁₋₁₃, PTH₁₋₁₄, PTH₁₋₁₅, PTH₁₋₁₆, PTH₁₋₁₇, PTH₁₋₁₈, PTH₁₋₁₉, PTH₁₋₂₀, PTH₁₋₂₁, PTH₁₋₂₂, PTH₁₋₂₃, PTH₁₋₂₄, PTH₁₋₂₅, PTH₁₋₂₆, PTH₁₋₂₇, PTH₁₋₂₈, PTH₁₋₂₉, PTH₁₋₃₀, PTH₁₋₃₁, PTH₁₋₃₂, PTH₁₋₃₃, PTH₁₋₃₄, PTH₁₋₃₅, PTH₁₋₃₆, PTH₁₋₃₇, PTH₂₋₅, PTH₂₋₆, PTH₂₋₇, PTH₂₋₈, PTH₂₋₉, PTH₂₋₁₀, PTH₂₋₁₁, PTH₂₋₁₂, PTH₂₋₁₃, PTH₂₋₁₄, or PTH₂₋₁₅, PTH₂₋₁₆, PTH₂₋₁₇, PTH₂₋₁₈, PTH₂₋₁₉, PTH₂₋₂₀, PTH₂₋₂₁, PTH₂₋₂₂, PTH₂₋₂₃, PTH₂₋₂₄, PTH₂₋₂₅, PTH₂₋₂₆, PTH₂₋₂₇, PTH₂₋₂₈, PTH₂₋₂₉, PTH₂₋₃₀, PTH₂₋₃₁, PTH₂₋₃₂, PTH₂₋₃₃, PTH₂₋₃₄, PTH₂₋₃₅, PTH₂₋₃₆, PTH₂₋₃₇, PTH₃₋₆, PTH₃₋₇, PTH₃₋₈, PTH₃₋₉, PTH₃₋₁₀, PTH₃₋₁₁, PTH₃₋₁₃, PTH₃₋₁₄, PTH₃₋₁₅, PTH₃₋₁₆, PTH₃₋₁₇, PTH₃₋₁₈, PTH₃₋₁₉, PTH₃₋₂₀, PTH₃₋₂₁, PTH₃₋₂₂, PTH₃₋₂₃, PTH₃₋₂₄, PTH₃₋₂₅, PTH₃₋₂₆, PTH₃₋₂₇, PTH₃₋₂₈, PTH₃₋₂₉, PTH₃₋₃₀, PTH₃₋₃₁, PTH₃₋₃₂, PTH₃₋₃₃, PTH₃₋₃₄, PTH₃₋₃₅, PTH₃₋₃₆, PTH₃₋₃₇, PTH₄₋₇, PTH₄₋₈~~.

~~PTH₄₋₉, PTH₄₋₁₀, PTH₄₋₁₁, PTH₄₋₁₂, PTH₄₋₁₃, PTH₄₋₁₄, PTH₄₋₁₅, PTH₄₋₁₆, PTH₄₋₁₇, PTH₄₋₁₈, PTH₄₋₁₉,
 PTH₄₋₂₀, PTH₄₋₂₁, PTH₄₋₂₂, PTH₄₋₂₃, PTH₄₋₂₄, PTH₄₋₂₅, PTH₄₋₂₆, PTH₄₋₂₇, PTH₄₋₂₈, PTH₄₋₂₉, PTH₄₋₃₀,
 PTH₄₋₃₁, PTH₄₋₃₂, PTH₄₋₃₃, PTH₄₋₃₄, PTH₄₋₃₅, PTH₄₋₃₆, PTH₄₋₃₇, PTH₅₋₈, PTH₅₋₉, PTH₅₋₁₀, PTH₅₋₁₁,
 PTH₅₋₁₂, PTH₅₋₁₃, PTH₅₋₁₄, PTH₅₋₁₅, PTH₅₋₁₆, PTH₅₋₁₇, PTH₅₋₁₈, PTH₅₋₁₉, PTH₅₋₂₀, PTH₅₋₂₁, PTH₅₋₂₂,
 PTH₅₋₂₃, PTH₅₋₂₄, PTH₅₋₂₅, PTH₅₋₂₆, PTH₅₋₂₇, PTH₅₋₂₈, PTH₅₋₂₉, PTH₅₋₃₀, PTH₅₋₃₁, PTH₅₋₃₂, PTH₅₋₃₃,
 PTH₅₋₃₄, PTH₅₋₃₅, PTH₅₋₃₆, or PTH₅₋₃₇.~~

6. (original): The isolated antibody of claim 1, wherein the binding between the antibody and the N-terminal sequence of whole PTH is dependent on the presence of amino acid residues 2-5 of the hPTH.

7. (original): The isolated antibody of claim 1, wherein the binding between the antibody and the N-terminal sequence of whole PTH is dependent on the presence of amino acid residues 3-6 of the hPTH.

8. (currently amended): The isolated antibody or antibody fragment of claim 1, wherein the ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment is a peptide having an amino acid sequence from between PTH₃₋₈₄ and PTH₃₄₋₈₄.

9. (currently amended): The isolated antibody of claim 1, wherein the ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment is a peptide having an amino acid sequence of human PTH₇₋₈₄.

10. (currently amended): A method for measuring a physiological level of whole parathyroid hormone (PTH) in a mammalian sample, which method comprises:

- a) obtaining a sample from a mammal to be tested;
- b) contacting said sample with an isolated antibody that specifically binds to an N-terminal sequence of whole PTH and is capable of detecting said whole PTH at a physiological level in said mammalian sample, with a proviso that said isolated antibody avoids binding to a ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment in said sample; and

c) assessing a complex formed between said whole ~~parathyroid hormone~~ PTH, if present in said sample, and said antibody, to measure physiological level of said whole ~~parathyroid hormone~~ PTH in said mammalian sample,

wherein said isolated antibody specifically binds to an epitope comprised in PTH₁₋₅, PTH₁₋₆, PTH₁₋₇, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₀, PTH₁₋₁₁, PTH₁₋₁₂, PTH₁₋₁₃, PTH₁₋₁₄ or PTH₁₋₁₅.

11. (original): The method of claim 10, wherein the sample is selected from the group consisting of a serum, a plasma and a blood sample.

12. (original): The method of claim 10, wherein the sample is a clinical sample.

13. (original): The method of claim 10 which is used for clinical management of renal disease subjects, subjects afflicted with osteoporosis or diagnosing primary hyperparathyroidism.

14. (original): The method of claim 10, wherein the mammal is a human.

15. (original): The method of claim 14, wherein the sample is a human clinical sample.

16. (currently amended): The method of claim 10, wherein the antibody is a monoclonal antibody, ~~or a~~ polyclonal antibody or an antibody fragment that specifically binds to whole PTH.

17. (previously presented): The method of claim 10, wherein the antibody specifically binds to an epitope comprised in PTH₁₋₆, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₂, or PTH₁₋₁₅.

18. (currently amended): The method of claim 10, wherein the antibody specifically binds to the ~~parathyroid hormone~~ PTH peptide human PTH₁₋₈, rat PTH₁₋₈, mouse PTH₁₋₈, bovine PTH₁₋₈, canine PTH₁₋₈, porcine PTH₁₋₈, horse PTH₁₋₈, human PTH₁₋₁₅, rat PTH₁₋₁₅, mouse PTH₁₋₁₅, bovine PTH₁₋₁₅, canine PTH₁₋₁₅, porcine PTH₁₋₁₅, or horse PTH₁₋₁₅, wherein at least four amino acids in said peptide sequence are part of a reactive portion with the antibody.

19–21. (canceled)

22. (currently amended): The method of claim 10, wherein the ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment is selected from the group consisting of PTH₃₋₈₄, PTH₄₋₈₄, PTH₅₋₈₄, PTH₆₋₈₄, PTH₇₋₈₄, PTH₈₋₈₄, PTH₉₋₈₄, PTH₁₀₋₈₄, PTH₁₁₋₈₄, PTH₁₂₋₈₄, PTH₁₃₋₈₄, PTH₁₄₋₈₄, PTH₁₅₋₈₄, PTH₁₆₋₈₄, PTH₁₇₋₈₄, PTH₁₈₋₈₄, PTH₁₉₋₈₄, PTH₂₀₋₈₄, PTH₂₁₋₈₄, PTH₂₂₋₈₄, PTH₂₃₋₈₄, PTH₂₄₋₈₄, PTH₂₅₋₈₄, PTH₂₆₋₈₄, PTH₂₇₋₈₄, PTH₂₈₋₈₄, PTH₂₉₋₈₄, PTH₃₀₋₈₄, PTH₃₁₋₈₄, PTH₃₂₋₈₄, PTH₃₃₋₈₄ and PTH₃₄₋₈₄.

23. (currently amended): The method of claim 10, wherein the ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment is a peptide having an amino acid sequence of human PTH₇₋₈₄.

24. (original): The method of claim 10, wherein the complex is assessed by a sandwich or competitive assay format.

25. (previously presented): The method of claim 24, wherein the antibody that specifically binds to an N-terminal sequence of whole PTH is used as a first antibody in a sandwich format assay, and a second antibody used in the sandwich format assay is an antibody that is capable of binding to a portion of whole PTH other than the N-terminal sequence to which the first antibody binds.

26. (original): The method of claim 25, wherein either the first antibody or the second antibody is attached to a surface and functions as a capture antibody.

27. (previously presented): The method of claim 26, wherein the capture antibody is attached to the surface directly.

28. (original): The method of claim 26, wherein the capture antibody is attached to the surface via a biotin-avidin (or streptavidin) linking pair.

29. (original): The method of claim 10, wherein the complex is assessed by a format selected from the group consisting of an enzyme-linked immunosorbent assay (ELISA), immunoblotting, immunoprecipitation, radioimmunoassay (RIA), immunostaining, latex agglutination, indirect hemagglutination assay (IHA), complement fixation, indirect immunofluorescent assay (IFA), nephelometry, flow cytometry assay, plasmon resonance assay, chemiluminescence assay, lateral flow immunoassay, u-capture assay, inhibition assay and avidity assay.

30. (previously presented): The method of claim 10, wherein the complex is assessed in a homogeneous assay format.

31. (currently amended): The method of claim 10, wherein the physiological level of whole ~~parathyroid hormone~~ PTH is less than 4 pmol/L.

32. (currently amended): The method of claim 10, wherein the physiological level of whole ~~parathyroid hormone~~ PTH is from about 0.2 pmol/L to about 4 pmol/L.

33. (original): The method of claim 10, which further comprises measuring a PTH peptide fragment level and/or total PTH level.

34. (original): The method of claim 33, wherein said sample is contacted with one or more isolated antibodies, and wherein each of said one or more isolated antibodies specifically bind one or more PTH peptide fragments selected from the group consisting of: PTH₃₉₋₈₄, PTH₁₋₃₄, PTH₄₃₋₆₈, PTH₇₋₈₄, PTH₃₉₋₆₈, PTH₅₃₋₈₄, PTH₆₅₋₈₄, PTH₄₄₋₆₈, PTH₁₉₋₈₄, PTH₂₃₋₈₄, PTH₁₋₃₈, PTH₁₋₄₈, PTH₁₋₅₈, PTH₁₋₆₈, and PTH₁₋₇₈.

35. (original): The method of claim 33, which further comprises comparing at least two parameters selected from the group consisting of the whole PTH level, total PTH peptide fragment level, total PTH level, C-terminal PTH fragment (cPTH) level, N-terminal PTH fragment level, and mid-terminal PTH fragment (mPTH) level.

36. (currently amended): The method of claim 35, wherein the results of said comparison are used to determine whether the mammal suffers from a bone turnover related disorder, ~~or to monitor bone disease or disorder related treatment.~~

37. (previously presented): The method of claim 36, which is used in the diagnosis or monitoring of treatment for adynamic bone disease or severe hyperparathyroidism.

38. (original): The method of claim 35, wherein the comparison is in the form of a ratio or proportion between the whole PTH level and the total PTH level.

39. (original): The method of claim 35, wherein the comparison is in the form of a ratio or proportion between the whole PTH level versus the combined total of the total PTH level minus the whole PTH level.

40-57. (canceled)

58. (original): The method of claim 10, which is used for:

- a) differentiating between a person having substantially normal parathyroid function and having hyperparathyroidism;
- b) monitoring parathyroid related bone disease and treatment;
- c) monitoring effects of therapeutic treatment for hyperparathyroidism; or
- d) diagnosing parathyroid related bone disease.

59. (currently amended): A kit for measuring a physiological level of whole parathyroid hormone (PTH) in a mammalian sample, which kit comprises, in a container, an isolated antibody that specifically binds to an N-terminal sequence of whole ~~parathyroid hormone~~ (~~PTH~~) and is capable of detecting said whole PTH at a physiological level in a mammalian sample, with a proviso that said isolated antibody avoids binding to a ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment in said sample, wherein said isolated antibody specifically binds to an epitope comprised in PTH₁₋₅, PTH₁₋₆, PTH₁₋₇, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₀, PTH₁₋₁₁, PTH₁₋₁₂, PTH₁₋₁₃, PTH₁₋₁₄ or PTH₁₋₁₅.

60–80. (canceled)

81. (currently amended): The method of claim 10, wherein the physiological level of whole ~~parathyroid hormone~~ PTH is from about 7 picogram/ml to about 39 picogram/ml.

82. (previously presented): The method of claim 26, wherein the capture antibody is attached to the surface indirectly.

83. (previously presented): The method of claim 10, wherein the complex is assessed in a heterogeneous assay format.

84. (currently amended): The method of claim 10, wherein the isolated antibody avoids binding greater than about 90% of a ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment in said sample.

85. (previously presented): The method of claim 10, wherein the isolated antibody specifically binds to an epitope comprised in PTH₁₋₅ or PTH₁₋₆.

86. (previously presented): The method of claim 25, wherein one of the first or the second antibody is labeled.

87. (currently amended): A method for measuring a physiological level of whole parathyroid hormone (PTH) in a mammalian sample, which method comprises:

- a) obtaining a sample from a mammal to be tested;
- b) contacting said sample with an isolated antibody that specifically binds to an N-terminal sequence of whole PTH and is capable of detecting said whole PTH at a physiological level in said mammalian sample, with a proviso that said isolated antibody avoids binding to a ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment; and

c) assessing a complex formed between said whole ~~parathyroid hormone~~ PTH, if present in said sample, and said antibody, to measure physiological level of said whole ~~parathyroid hormone~~ PTH in said mammalian sample,

wherein said antibody specifically binds to an epitope comprised in PTH₁₋₆, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₂, PTH₁₋₁₅, or PTH₃₋₁₂.

88. (currently amended): The method of claim 87, wherein the ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment is a peptide having an amino acid sequence of human PTH₇₋₈₄.

89. (currently amended): A method for measuring a physiological level of whole parathyroid hormone (PTH) in a mammalian sample, which method comprises:

a) obtaining a sample from a mammal to be tested;

b) contacting said sample with an isolated antibody that specifically binds to an N-terminal sequence of whole PTH and is capable of detecting said whole PTH at a physiological level in said mammalian sample, with a proviso that said isolated antibody avoids binding to a ~~non-whole~~ a non-(1-84) or non-(1-86) PTH fragment; and

c) assessing a complex formed between said whole ~~parathyroid hormone~~ PTH, if present in said sample, and said antibody, to measure physiological level of said whole ~~parathyroid hormone~~ PTH in said mammalian sample,

wherein said antibody specifically binds to the ~~parathyroid hormone~~ PTH peptide human PTH₁₋₈, rat PTH₁₋₈, mouse PTH₁₋₈, bovine PTH₁₋₈, canine PTH₁₋₈, porcine PTH₁₋₈, horse PTH₁₋₈, human PTH₁₋₁₅, rat PTH₁₋₁₅, mouse PTH₁₋₁₅, bovine PTH₁₋₁₅, canine PTH₁₋₁₅, porcine PTH₁₋₁₅, or horse PTH₁₋₁₅, wherein at least four amino acids in said peptide sequence are part of a reactive portion with the antibody.

90. (currently amended): The method of claim 89, wherein the ~~non-whole~~ non-(1-84) or non-(1-86) PTH fragment is a peptide having an amino acid sequence of human PTH₇₋₈₄.

91. (currently amended): The method of claim 10, wherein the isolated antibody that specifically binds to an N-terminal sequence of whole PTH is produced by immunizing a mammal

with whole PTH, collecting the antibody from the mammal and isolating the antibody by binding the antibody to an epitope comprised in PTH₁₋₅, PTH₁₋₆, PTH₁₋₇, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₀, PTH₁₋₁₁, PTH₁₋₁₂, PTH₁₋₁₃, PTH₁₋₁₄ or PTH₁₋₁₅, and the isolated antibody specifically binds to whole PTH.

92. (previously presented): The method of claim 91, wherein the mammal is a goat.

93. (previously presented): The method of claim 91, wherein the whole PTH is human whole PTH and the peptide is a human or rat PTH peptide.

94. (previously presented): The method of claim 91, wherein the whole PTH is rat whole PTH and the peptide is a human or rat PTH peptide.

95. (previously presented): The method of claim 10, wherein the mammal is a rat.

96. (currently amended): The method of claim 10, wherein the isolated antibody that specifically binds to an N-terminal sequence of whole PTH is produced by immunizing a mammal with whole PTH, collecting the antibody from the mammal and isolating the antibody using a peptide selected from the group consisting of PTH₁₋₅, PTH₁₋₆, PTH₁₋₇, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₀, PTH₁₋₁₁, PTH₁₋₁₂, PTH₁₋₁₃, PTH₁₋₁₄ and PTH₁₋₁₅, and the isolated antibody specifically binds to whole PTH.

97. (new): The method of claim 35, wherein the results of said comparison are used to monitor bone disease or disorder related treatment.

98. (new): The isolated antibody or antibody fragment of claim 8, wherein the non-(1-84) or non-(1-86) PTH fragment is selected from the group consisting of PTH₄₋₈₄, PTH₅₋₈₄, PTH₆₋₈₄, PTH₇₋₈₄, PTH₈₋₈₄, PTH₉₋₈₄, PTH₁₀₋₈₄, PTH₁₁₋₈₄, PTH₁₂₋₈₄, PTH₁₃₋₈₄, PTH₁₄₋₈₄ and PTH₁₅₋₈₄.

99. (new): The method of claim 22, wherein the non-(1-84) or non-(1-86) PTH fragment is selected from the group consisting of PTH₄₋₈₄, PTH₅₋₈₄, PTH₆₋₈₄, PTH₇₋₈₄, PTH₈₋₈₄, PTH₉₋₈₄, PTH₁₀₋₈₄, PTH₁₁₋₈₄, PTH₁₂₋₈₄, PTH₁₃₋₈₄, PTH₁₄₋₈₄ and PTH₁₅₋₈₄.